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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,099	01/05/2000	ANTHONY P. ADAMIS	50069/002002	1198

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/478,099	ADAMIS ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 January 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0903*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed September 22, 2003 (hereinafter referred to as "the response") has been entered. Claims 5, 12, and 14 have been amended.

Claims 1-18 and 21 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

The rejections of Claims 1-18 and 21 under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments to the claims.

The rejection of Claims 1-7, 11, and 18 under 35 U.S.C. 102(b) as being anticipated by Matsuo et al. (1996) is withdrawn in view of the amendments to Claims 5-7, 11, and 18 and the arguments presented at page 10 of the response. Specifically, Applicants argue that the authors speculate that "[l]iposomes might penetrate the cornea, diffuse in the intraocular fluid, and then reach the retina" (page 948). Thus, the Examiner finds that there is no disclosure that the nucleic acid actually **passes through the sclera,** as required by the claims.

The rejection of Claim 15 under 35 U.S.C. 103(a) as being unpatentable over Matsuo et al. (1996) and Faktorovich et al. (1990) is withdrawn in view of the amendment to Claim 5 from which Claim 15 depends, and the arguments presented at pages 10 and 11 of the response. Specifically, Applicants argue that the authors speculate that "[l]iposomes might penetrate the cornea, diffuse in the intraocular fluid, and then reach the retina" (page 948). Thus, the Examiner finds that there is no disclosure that the nucleic acid actually **passes through the sclera,** as required by the claims. At page 11, paragraph 4 of the response, Applicants argue that there would have been no reasonable expectation that the nucleic acid

would be able to pass through the sclera. At page 11, paragraph 3 of the response, Applicants argue that the composition of the liposomes used in their method has a significant effect on the transport of the gene into the eye. Applicants conclude that the skilled artisan would have no reason to believe that "a nucleic acid in the **absence** of a particular liposome formation" (emphasis added) would be capable of being transported into the eye and Applicants further submit that such liposome formulations are not required by the claimed method. Applicants are arguing limitations that are not in the claims. The claims **do not** exclude the use of a nucleic acid-liposome composition. There is nothing in the claims requiring the "**absence**" of liposomes as Applicants argue. The claims clearly encompass the use of liposomes.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claim 21 stands rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth on pages 2-3 of the Office Action mailed 6/3/03, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The newly added claim includes new matter.

Claim 21 recites elements without support in the original disclosure, thereby adding new matter to the claims. Claim 21 refers to a nucleic acid that reduces development of choroidal neovascularization. However, the specification fails to provide support for a nucleic acid that reduces development of choroidal neovascularization. As support for the newly added claim, Applicants point to the specification at page 34, lines 10-14, but this section does not provide support for a nucleic acid that reduces

development of choroidal neovascularization. Thus, Applicants have not pointed to adequate support for this amendment in the specification as-filed and the Examiner does not find specific support for this amendment.

At page 4 of the response, Applicants state that support for Claim 21 can be found at page 6, lines 17-23, page 7, lines 8-10, and page 8, lines 2-4. However, the cited sections do not refer to a nucleic acid that reduces development of choroidal neovascularization. At pages 6-7, the specification states that the therapeutic agent can be a polypeptide, particularly an antibody, nucleic acid, synthetic organic molecule, or naturally occurring organic molecule. At page 34, lines 10-14 (cited by Applicants as support for the newly added claim), the specification specifically refers to an anti-VEGF antibody. However, the specification does not specifically refer to a nucleic acid that reduces development of choroidal neovascularization.

Thus, the rejection is maintained.

Enablement

Claims 1-18 and 21 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action of Paper No. 10 (mailed 8/15/01), pages 3-8 of the Office Action of Paper No. 13 (mailed 5/21/02), and pages 3-4 of the Office Action mailed 6/3/03, and for the reasons set forth herein below, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 5 of the response, Applicants argue that the specification clearly discloses how to apply a nucleic acid to a scleral surface and that "this is all that is required by the claimed invention." The Examiner does not agree because it is well established in our law that the specification must teach how to use the claimed invention. The claims also require that the nucleic acid must pass through the sclera into

the interior of the eye. Claims 16, 17, and 21 explicitly require that the method provide a therapeutic effect for a variety of retinal or choroidal diseases.

At page 6 of the response, Applicants argue that those skilled in the art were motivated to administer nucleic acids into the eye. Applicants point to Leeds et al. (1997) for describing the intravitreal injection of an oligonucleotide, ISIS 2922, for treatment of CMV-induced retinitis. Applicants also point to Robinson et al. (1996) for disclosing a VEGF antisense oligonucleotide that, when injected intravitreally, can inhibit retinal neovascularization in a murine model of proliferative retinopathy. Applicants also point to WO 97/15330 for describing oligonucleotides that one of skill in the art might want to deliver to the eye. In view of these three articles which describe oligonucleotides that the skilled artisan might want to deliver to the interior of the eye, at least for reasearch purposes, the Examiner agrees that alternate methods of oligonucleotide delivery to the interior of the eye would have use in the art. However, the Examiner does not agree that the instantly claimed method is enabled due to the unpredictability in the gene delivery art, for reasons of record advanced in the previous Office Actions. The instant specification does not provide a working example of the claimed invention and the evidence submitted by Applicants to demonstrate operability of the claimed method (i.e., the poster submitted in the response of November 20, 2002 and the article of Carrasquillo (2003) submitted as reference C18) describes experiments that were not carried out in accordance with the teachings of the specification. The poster and article describe the use of poly(lactic-co-glycolic)acid microspheres for the delivery of an oligonucleotide by transscleral delivery, but the instant specification does not. Furthermore, the poster indicates that the oligonucleotide-loaded microsphere is about 50 kDa. Thus, the evidence submitted does not demonstrate that nucleic acids as large as 150 kDa can be delivered transsclerally. Moreover, the evidence does not demonstrate delivery without a "means for facilitating transport of the nucleic acid across the sclera."

At page 7 of the response, Applicants assert that there is no need for a means or device for facilitating transport of the nucleic acid across the sclera. No support is offered for this assertion. Applicants argue that Matsuo et al. (1996) discloses the use of a nucleic acid far larger than those recited in the pending claims. The Examiner agrees that the nucleic acid of Matsuo et al. is larger than 150 kDa, but that does not obviate the fact that neither the prior art nor the instant specification teaches how to achieve transport of a nucleic acid across the sclera in the absence of a means for facilitating the transport. No evidence has been submitted to demonstrate that smaller nucleic acids, of the size of 150 kDa and smaller, can be delivered across the sclera without a means for facilitating transport.

Thus, the enablement rejection is maintained.

Written Description

Claims 1-18 and 21 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 8-10 of the Office Action of Paper No. 13 (mailed 5/21/02), pages 4-5 of the Office Action of Paper No. 22 (mailed 6/3/03), and for the reasons discussed herein below, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

At page 8, paragraph 1 of the response, Applicants argue that the specification provides a written description of the claimed methods on pages 5-7, 9, 13 and Example 1. However, the written description rejection is based on lack of description of a **nucleic acid** molecule that could be used in practicing the method of the invention, for diagnostic or therapeutic purposes (see pages 9-10 of the Office Action mailed 5/21/02). The nucleic acid molecule is an essential element of the claimed invention. None of the sections cited by Applicants describe a nucleic acid molecule that can be used in the claimed method. On

the contrary, Example 1 of the specification is exclusively limited to testing fluorescent compounds conjugated to immunoglobulins, proteins, and dextran (see Table 1 on page 20). The experiments were carried out *in vitro* using rabbit sclera.

At page 8, paragraph 2 of the response, Applicants state that the amendment to Claim 5, providing an upper size limit on the nucleic acid, obviates the rejection of Claim 5 and the claims depending therefrom. Applicants are reminded, however, that all claims, including those claims reciting an upper size limit, are rejected for lack of written description. Thus, adding an upper size limit to Claim 5 does not obviate the rejection. The specification does not describe a nucleic acid of any size that can be used in the claimed method.

At page 8, paragraph 3 of the response, Applicants state that the teachings on pages 6, lines 17-23 and in the paragraph bridging pages 7 and 8 of the specification demonstrate that Applicants were in possession of the invention defined by claims 16 and 17. The section on page 6 reads as follows:

> In still other embodiments of the above aspects the mammal is human. The method is used to treat a retinal or choroidal disease. In preferred embodiments, the retinal or choroidal disease is selected from the group consisting of macular degeneration, diabetic retinopathy, retinitis pigmentosa and other retinal degenerations, retinal vein occlusions, sickle cell retinopathy, glaucoma, choroidal neovascularization, retinal neovascularization, retinal edema, retinal ischemia, proliferative vitreoretinopathy, and retinopathy of prematurity.

Thus, it is clear that this section does not describe any nucleic acids that can be used to treat the various diseases mentioned. The paragraph bridging pages 7-8 reads as follows:

> By "retinal or choroidal disease" is meant a disease or condition in which the retina or choroid function in a diminished capacity as compared to a subject without such a condition, or as compared to the subject itself prior to the onset of the condition or disease. Examples of retinal or choroid diseases include, but are not limited to macular degeneration, diabetic retinopathy, retinitis pigmentosa and other retinal degenerations, retinal vein occlusions, sickle cell retinopathy, glaucoma, choroidal neovascularization, retinal neovascularization, retinal edema, retinal ischemia, proliferative vitreoretinopathy, and retinopathy of prematurity.

Again, it is clear that this section does not describe any nucleic acids that can be used therapeutically and delivered by the method of the claimed invention to treat the various diseases mentioned. Rather it is left

to the skilled artisan to come up with nucleic acids that could be used to treat the various diseases mentioned in the specification and claims.

At page 8, paragraph 1 and 3 of the response, Applicants again refer to the poster evidence submitted on November 20, 2002. Applicants are reminded that the specification itself must provide a written description of the claimed invention. Applicants cannot rely on a post-filing submission to provide a written description of the claimed invention. Sufficiency under the first paragraph of 35 U.S.C. 112 must be judged as of the filing date.

Applicants have not addressed the stated grounds for rejection, which is based on the fact that the specification does not describe any nucleic acid molecule that can be used in the claimed method.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER